REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Claims 1-57, 59-61, and 63-79 have been canceled. Claims 80-104 are new. After entry of the Amendment, claims 58, 62, and 80-104 are pending.

Applicants submit the newly presented claims are supported throughout the specification, for example at page 15, lines 1-19; at page 24, lines 3-5; at page 26, line 23 to page 27, line 2; at page 28, lines 22-26; at pages 71 and 72; Example 21 at page 113; and Figure 21; and raise no issues of new matter.

Due to the number of restriction groups and the Examiner rejoining certain claims to Group I, Applicants are unsure of the status of the antagonist linking claim (claim 62) and elected species. For purposes of responding to the Office Action, Applicants believe the elected species is "antagonist antibodies". Applicants remind the Examiner that upon indication of allowable subject matter, any claims directed to non-elected species must be rejoined or reinstated and fully examined for patentability. MPEP § 809. To further prosecution, the pending claims are drawn to antagonist antibodies that specifically bind EG-VEGF.

Informalities in Disclosure

The Examiner objected to the disclosure because of several informalities in the text of the specification. Applicants have corrected the informalities suggested by the Examiner, including spelling errors and accession numbers. Withdrawal of this objection is respectfully requested.

Non-Elected Embodiments

The Examiner objected to claims 11, 14, 17, and 63 as encompassing non-elected embodiments. This objection has been obviated by cancellation of the objected claims and submission of new claims drawn to the elected species, antibody antagonists. Withdrawal of the objection is respectfully requested.

Deposit of Materials

Claims 1-18, 20-24, and 62-79 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner alleges the hybridomas secreting the claimed monoclonal antibodies are not publicly available. Claims 1-18, 2-24, and 63-79 have been canceled. Applicants address this rejection insofar as it applies to claim 62 and the newly presented claims.

The Examiner required amendment of the specification to include the date of deposit of the hybridomas and the complete name and address of the depository. Applicants submit amendment of the specification is not necessary as this information was included in the application as filed at page 118, line 5 to page 119, line 4.

To satisfy the deposit requirement for deposits made under the Budapest Treaty, a statement that all restrictions imposed by the depositor on the availability to the public of the deposited biological material will be irrevocably removed upon the granting of the patent is submitted herewith to satisfy the deposit requirements under 37 CFR §§ 1.803-1.808.

Applicants respectfully request withdrawal of the enablement rejection.

Enablement

The Examiner rejected claims 1-18, 20-24, and 62-79 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. Applicants respectfully traverse this rejection. Claims 1-18, 20-24, and 63-79 have been canceled. Applicants discuss this rejection insofar as it applies to claim 62 and might apply to the newly presented claims.

The Examiner asserts the specification does not provide sufficient guidance and working examples to enable the claims. Applicants do not agree and submit that the specification provides sufficient guidance and working examples to enable the production and use of antibodies that specifically bind EG-VEGF. The standard for an enabling disclosure requires a reasonable correlation to the scope of the claims.

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. *In re Fischer*, 427 F.2d 833, 839 (CCPA 1970).

The specification contains sufficient disclosure to enable the production of specific antibodies raised against specific antigens. Example 1 describes how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding computer algorithm used to identify the cDNA clones. Examples 2-6 teach expression of EG-VEGF. Example 7 describes production of antibodies that specifically bind EG-VEGF. Specific nucleic acid sequences encoding EG-VEGF (nucleotides 91-405 of SEQ ID NO:1 and SEQ ID NO:3) and amino acid sequence (SEQ ID NO:2) of EG-VEGF are taught in the specification. Example 21 describes methods and sequences used to immunize mice with EG-VEGF and generate seven monoclonal antibodies that bound EG-VEGF. Four of the monoclonal antibodies had demonstrated neutralizing activity (Example 21 and Figure 21).

The Examiner objected to the scope of the claimed antibodies. In support of the rejection, he asserts that the specification only teaches four monoclonal antibodies (1C6, 4H9, 2A3, and 2A8) and alleges that only antibodies 1C6 and 4H9 have neutralizing activity in a cell based proliferation assay. Applicants do not agree.

In cell based proliferation assays, antibodies 1C6, 2A3, 2A8, and 4H9 each inhibited proliferation of endothelial cells induced by EG-VEGF. See, for example, Figure 21 and the specification at page 114, lines 5-8:

> As shown in Figure 21, four antibodies were found to neutralize EG-VEGF activity. These were antibodies 1C6, 2A3, 2A8, and 4H9. In particular, monoclonal antibody 4H9 was found to completely neutralize the activity of 10 nM EG-VEGF when added at a dose of 10 μg/ml or higher.

Figure 21 clearly shows that antibodies 2A3 and 2A8 have neutralizing activity. Antibody 2A3 had neutralizing activity at least at 10 μg/ml and 25 μg/ml and antibody 2A8 had neutralizing activity at least at 25 μg/ml and 50 μg/ml (Figure 21).

The Examiner further alleges the recent failures in clinical trials using a VEGF antagonist indicate the unpredictability of angiogenesis inhibitors for cancer treatment. As a preliminary matter, Applicants note the claims currently under examination are drawn to antibodies that specifically bind EG-VEGF and not methods of treating cancer with anti-EG-VEGF antibodies. Also, in contrast to the Examiner's opinions regarding VEGF antagonists, the VEGF antagonist antibody AVASTIN™ was recently approved by the FDA for the treatment of cancer (see enclosed press release).

Applicants submit the specification fully enables the claims. The USPTO has acknowledged that production of antibodies against a characterized antigen is a well developed and mature technology where the level of skill is high and advanced (see, for example, Example 16 in the Revised Written Description Guidelines Training Materials). Considering the high and advanced level of skill in the art and the guidance and working examples provided in the specification, Applicants assert one of skill in the art would be able to make and use the antibodies and compositions as claimed without undue experimentation.

Written Description

The Examiner rejected claims 1-18, 20-24, and 62-79 under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants respectfully traverse this rejection. Claims 1-18, 20-24, and 63-79 have been canceled. Applicants discuss this rejection insofar as it applies to claim 62 and the newly presented claims.

The Examiner alleges the specification does not reasonably provide a written description of any anti-EG-VEGF antibody, such as 1C6, 2A3, 2A8, and 4H9, and fails to provide a representative number of species to describe the genus. Applicants do not agree.

Reference in the specification to a deposit in a public depository constitutes an adequate written description of the deposited material sufficient to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. *Enzo Biochem. v. Gen-Probe*, 296 F.3d 1316, 1325 (Fed. Cir. 2002). The clone encoding SEQ ID NO:1 and the hybridomas that produce antibodies 1C6, 2A3, 2A8, and 4H9 were deposited with the American Type Culture Collection as described in the specification at page 118. Applicants therefore respectfully submit the written description rejection at least as it applies to antibodies 1C6, 2A3, 2A8, and 4H9 should be withdrawn.

Applicants also direct the Examiner's attention to Example 16 in the USPTO Revised Written Description Guidelines Training Materials. Example 16 outlines a written description analysis of an antibody claim that satisfies the requirement under 35 U.S.C. § 112, first paragraph. The claim in Example 16 is directed to a genus of antibodies capable of binding antigen X. The specification provided a clear protocol by which antigen X was isolated. Antigen X was purified by gel filtration and found to have a molecular weight of 55 KD. The

specification did not disclose antibodies that specifically bind antigen X in an example. Example 16 in the written description guidelines states:

> Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.

Applying the analysis set forth in Example 16 of the written description guidelines, Applicants submit the specification sufficiently describes the genus of antibodies claimed. Similar to the claim analyzed in Example 16, Applicants' claims are directed to a genus of antibodies that specifically bind EG-VEGF. Example 1 in Applicants' specification describes how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding computer algorithm used to identify the cDNA clones. Examples 2-6 teach expression of EG-VEGF. Example 7 describes production of antibodies that specifically bind EG-VEGF. Specific nucleic acid sequences encoding EG-VEGF (nucleotides 91-405 of SEQ ID NO:1 and SEQ ID NO:3) and amino acid sequence (SEQ ID NO:2) of EG-VEGF are taught in the specification. Example 21 describes methods and sequences used to immunize mice with EG-VEGF and generate seven monoclonal antibodies that bound EG-VEGF.

In view of the foregoing, Applicants submit the specification sufficiently complies with the written description requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of the this rejection is respectfully requested.

New Matter

The Examiner rejected claims 1-10, 15-16, 23-24, and 70-73 under 35 U.S.C. § 112, first paragraph, as containing new matter. These claims have been canceled and the new claims recite the monoclonal antibodies with their ATCC accession numbers. Withdrawal of this rejection is respectfully requested.

Indefiniteness

The Examiner rejected claims 1-10, 15-16, 23-24, 65, and 70-73 under 35 U.S.C. § 112, second paragraph, as indefinite. These claims have been canceled. Applicants note the monoclonal antibodies are referred to by accession numbers in the newly presented claims. Withdrawal of this rejection is respectfully requested.

Anticipation

Claims 2, 7, 10-14, 16, 18, 20-22, 62-64, 68-69, 74-76, and 78-79 were rejected under 35 U.S.C. §102(b) as anticipated by Brekken et al., 1998, *Cancer Res.*, 58:1952-1959. Applicants respectfully traverse this rejection. Claims 2, 7, 10-14, 16, 18, 20-22, 63, 64, 68, 69, 74-76, 78, and 79 have been canceled. Applicants discuss this rejection insofar as it applies to claim 62 and the newly presented claims.

To anticipate a claim, each and every element of the claim must be described, either expressly or inherently, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The Brekken reference teaches antibodies to VEGF and VEGF:receptor complex. VEGF and EG-VEGF are different molecules having different amino acid sequences. The cited reference does not describe EG-VEGF and does not teach anti-VEGF antibodies that specifically bind **EG-VEGF**.

The Brekken reference fails to disclose the claimed invention and therefore does not anticipate the claims. Accordingly, withdrawal of the anticipation rejection is respectfully requested.

Obviousness

The Examiner rejected numerous claims under 35 U.S.C. § 103(a) as unpatentable over the primary reference of Brekken et al. in view of the secondary references of Harlow et al., Antibodies A Laboratory Manual, Cold Spring Harbor, NY, 1988, pages 626-629; U.S. Patent No. 6,180,370B; U.S. Patent No. 6,132,729; U.S. Patent No. 5,858,682; or U.S. Patent No. 4,946,778. Applicants respectfully traverse this rejection. Claims 1-18, 20-24, and 63-79 have been canceled. Applicants discuss this rejection insofar as it applies to claim 62 and the newly presented claims.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP § 2142. Three criteria must be met by the Examiner to establish a prima facie case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). The Examiner has failed to establish the cited combination of references teaches or suggest all the limitations of Applicants' claims.

As discussed above, the primary Brekken reference does not teach EG-VEGF or anti-EG-VEGF antibodies. None of the secondary references cited by the Examiner cure the deficiencies of the primary Brekken reference. None of the cited secondary references teach or suggest EG-VEGF or anti-EG-VEGF antibodies.

Applicants therefore submit the Examiner has not established a *prima facie* case of obviousness. The Examiner has failed to establish the combination of Brekken et al. and any of the cited secondary references teaches or suggests all the limitations of the claims. Accordingly, withdrawal of the obviousness rejection is respectfully requested.

Conclusion

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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